

? s (tumor? or cancer? or malignan?) (5n) (cell(w)line??)

Processing

1508425 TUMOR?
1174877 CANCER?
472958 MALIGNAN?
4513960 CELL
2446750 LINE??

S1 98795 (TUMOR? OR CANCER? OR MALIGNAN?) (5N) (CELL(W)LINE??)

? s her(w)2 or neu or erb(w)2

Processing

90118 HER
10040468 2
5752 HER(W)2
13184 NEU
3989 ERB

10040468 2
602 ERB(W)2

S2 14666 HER(W)2 OR NEU OR ERB(W)2

? s s1 and s2

98795 S1
14666 S2

S3 1415 S1 AND S2

? s ctl??

S4 36430 CTL??

? s s3 and s4

1415 S3
36430 S4

S5 72 S3 AND S4

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...examined 50 records (50)

...completed examining records

S6 34 RD (unique items)

? s s6 and py<=1995

Processing

34 S6
27411514 PY<=1995
S7 7 S6 AND PY<=1995

? t s7/3,k,ab/1-7

7/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

08672829 96025911 PMID: 7594611

Tumor-specific and HLA-A2-restricted cytotoxicity by tumor-associated lymphocytes in human metastatic breast cancer.

Linehan D C; Goedegebuure P S; Peoples G E; Rogers S O; Eberlein T J

Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Nov 1 1995, 155 (9) p4486-91, ISSN 0022-1767 Journal Code: 2985117R

Contract/Grant No.: CA 09535; CA; NCI; CA606662; CA; NCI; RO1 CA45484; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

A tumor-specific cytotoxic T lymphocyte (CTL) immune response has been well documented in melanoma, renal cell carcinoma, and ovarian cancer. Conflicting evidence exists regarding the existence of tumor-specific CTL populations in breast cancer. Tumor cells and tumor-associated

lymphocytes (TAL) were isolated from the pleural effusions of six consecutive patients with metastatic breast cancer. After solid-phase anti-CD3 stimulation, TAL cultures were expanded with weekly autologous tumor stimulation and low-dose IL-2 for 3 wk. T cell populations were characterized using flow cytometric analysis and ranged from 49 to 91% CD8+, > 98% CD3+, and < 3% CD16+. Functionally, tumor-stimulated TAL showed tumor-specific recognition of autologous tumor cells (241 +/- 142 LU20/10(7)) and no detectable lysis of autologous fibroblasts, Daudi or K562. Cytotoxicity of TAL against HLA-A2+ allogeneic targets was significantly higher when compared with HLA-A2- tumor cell lines (127 +/- 76 vs 6 +/- 18 LU, p = 0.0001). This cytotoxicity against autologous and allogeneic tumor cells was blocked by anti-HLA-A2 mAb and cold HLA-A2+ targets in cold-target inhibition assays. TAL from all HLA-A2+ patients recognized GP2, a known, HER2/neu-derived tumor-associated peptide Ag that is HLA-A2 restricted. We have shown that TAL obtained from metastatic effusions of breast cancer patients contain lymphocytes that can recognize and lyse autologous and allogeneic tumor cells in a tumor-specific, HLA-A2-restricted fashion. In addition, tumor-specific TAL derived from breast cancer patients can selectively lyse HLA-A2+ pancreatic and ovarian tumor cell targets, suggesting a common HLA-A2-restricted tumor-associated Ag between these distinct epithelial cancers. Further elucidation of the cell-mediated immune response to breast cancer and the identification of shared TAA could result in the development of broadly applicable vaccine therapies for many cancers.

Nov 1 1995,

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... cold-target inhibition assays. TAL from all HLA-A2+ patients recognized GP2, a known, HER2/neu-derived tumor-associated peptide Ag that is HLA-A2 restricted. We have shown that TAL...

7/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08626708 95385100 PMID: 7656335

Shared T cell epitopes in epithelial tumors.

Peoples G E; Smith R C; Linehan D C; Yoshino I; Goedegebuure P S; Eberlein T J

Laboratory of Biological Cancer Therapy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Cellular immunology (UNITED STATES) Sep 1995, 164 (2) p279-86,
ISSN 0008-8749 Journal Code: 1246405

Contract/Grant No.: CA09535; CA; NCI; R01 CA45484; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have previously shown the importance of human leukocyte antigen (HLA)-A2 and the proto-oncogene HER2/neu in the T cell recognition of ovarian cancer. Since these proteins are ubiquitously expressed in epithelial-derived tumors, we have acid-eluted HLA-bound peptides from ovarian cancers, fractionated the peptides, and reconstituted T cell epitopes on the HLA-A2+ T2 cell line to determine if common tumor-associated antigens exist among HLA-A2+, HER2/neu +

epithelial cancers. We demonstrate that tumor-specific cytotoxic T lymphocytes (CTL) generated from tumor-infiltrating lymphocytes isolated from three ovarian, two breast, and two non-small-cell lung cancers recognize at least three of the same peptide fractions from multiple elutions. One of these peptide fractions coelutes with a HER2/neu-derived peptide which has been shown recently to be recognized by these same CTL. These findings demonstrate that a common peptide-based tumor vaccine is theoretically possible for many different epithelial-derived cancers.

Sep 1995,

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7/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08147112 94282743 PMID: 7912166

HER2/neu-derived peptides are shared antigens among human non-small cell lung cancer and ovarian cancer.

Yoshino I; Goedegebuure P S; Peoples G E; Parikh A S; DiMaio J M; Lyster H K; Gazdar A F; Eberlein T J

Division of Surgical Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115.

Cancer research (UNITED STATES) Jul 1 1994, 54 (13) p3387-90,
ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: ROI CA09535; CA; NCI; ROI CA45484; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Previously, we have reported a correlation between the expression of HER2/neu and sensitivity to HLA-A2-restricted cytotoxic T-cells (CTL) in ovarian cancer. To investigate the role of HER2/neu in human non-small cell lung cancer (NSCLC), we established autologous tumor-specific CTL from tumor-infiltrating lymphocytes of HLA-A2+ HER2/neu+ NSCLC patients. These CTL lines specifically recognized HLA-A2+ HER2/neu + autologous and allogeneic NSCLC cell lines as well as HLA-A2+ HER2/neu+ heterologous ovarian cancer cell lines. Furthermore, these CTL recognized an overexpressed, HER2/neu-derived peptide. From these results, we conclude that HLA-A2 serves as a restriction element in NSCLC. More importantly, at least one HER2/neu-derived peptide is a tumor-associated antigen in NSCLC and ovarian cancer.

HER2/neu-derived peptides are shared antigens among human non-small cell lung cancer and ovarian cancer.

Jul 1 1994,

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7/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08052676 94179821 PMID: 8133050

Association of HER2/neu expression with sensitivity to tumor-specific CTL in human ovarian cancer.

Yoshino I; Peoples G E; Goedegebuure P S; Maziarz R; Eberlein T J
Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Mar 1 1994, 152 (5) p2393-400, ISSN 0022-1767 Journal Code: 2985117R

Contract/Grant No.: CA 09535; CA; NCI; RO1 CA 45484; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

To study potential sources of tumor-associated Ags in human ovarian cancer, we have established two ovarian tumor cell lines (OvS1 and OvA2) from two ovarian cancer patients, which express the cellular oncogene HER2/neu. Corresponding tumor infiltrating lymphocyte cultures have also been established and display an autologous tumor-specific pattern of cytotoxicity that is HLA-A2 restricted. To determine the potential relationship between HER2/neu expression and CTL-mediated cytotoxicity, we first established tumor cell clones from OvS1. These were categorized as high or low expressors of HER2/neu (cOvS1+ or cOvS1-, respectively), and cOvS1+ clones displayed a significantly higher sensitivity to CTL killing as compared with cOvS1- clones. To modulate the expression of HER2/neu, ovarian cancer cells were treated with IFN-gamma. After this exposure, HER2/neu expression was significantly decreased, whereas the expression of HLA Class I was significantly increased. Despite the increase in HLA Class I molecules on the cell surface, CTL-mediated cytotoxicity of both OvS1 and OvA2 was significantly decreased. IFN-gamma treated cOvS1+ clones displayed a similar decrease in sensitivity to CTL killing, whereas IFN-gamma treated cOvS1- clones displayed an increase or no change in sensitivity to CTL. To confirm this apparent association between HER2/neu expression and CTL recognition, melanoma tumor cell lines that were insensitive to ovarian tumor-specific CTL were transfected with the HER2/neu gene. An HLA-A2+ HER2/neu-transfected melanoma cell line was made sensitive to HLA-A2 restricted ovarian tumor-specific CTL but not to HLA-A2 unrestricted CTL, whereas an HLA-A2- HER2/neu-transfected melanoma remained insensitive to HLA-A2 restricted CTL. These results demonstrate that the sensitivity of ovarian epithelial tumor cells to CTL-mediated lysis is associated with the level of expression of HER2/neu, suggesting that this oncogene product may serve as a source of tumor-associated Ags or as an inducer of such peptides. This is the first time in a human tumor system that oncogene expression has been related to the induction of antigenicity. These results prompt us to approach new strategies for immunotherapy of cancer.

Association of HER2/neu expression with sensitivity to tumor-specific CTL in human ovarian cancer.

Mar 1 1994,

... potential sources of tumor-associated Ags in human ovarian cancer, we have established two ovarian tumor cell lines (OvS1 and OvA2) from two ovarian cancer patients, which express the cellular oncogene HER2/neu. Corresponding tumor infiltrating lymphocyte cultures have also been established and display an autologous tumor-specific pattern of cytotoxicity that is HLA-A2 restricted. To determine the potential relationship between HER2/neu expression and CTL-mediated cytolysis, we first established tumor cell clones from OvS1. These were categorized as high or low expressors of HER2/neu (cOvS1+ or cOvS1-, respectively), and cOvS1+ clones displayed a significantly higher sensitivity to CTL killing as compared with cOvS1- clones. To modulate the expression of HER2/neu, ovarian cancer cells were treated with IFN-gamma. After this exposure, HER2/neu expression was significantly decreased, whereas the expression of HLA Class I was significantly increased. Despite the increase in HLA Class I molecules on the cell surface, CTL-mediated cytolysis of both OvS1 and OvA2 was significantly decreased. IFN-gamma treated cOvS1+ clones displayed a similar decrease in sensitivity to CTL killing, whereas IFN-gamma treated cOvS1- clones displayed an increase or no change in sensitivity to CTL. To confirm this apparent association between HER2/neu expression and CTL recognition, melanoma tumor cell lines that were insensitive to ovarian tumor-specific CTL were transfected with the HER2/neu gene. An HLA-A2+ HER2/neu-transfected melanoma cell line was made sensitive to HLA-A2 restricted ovarian tumor-specific CTL but not to HLA-A2 unrestricted CTL, whereas an HLA-A2- HER2/neu-transfected melanoma remained insensitive to HLA-A2 restricted CTL. These results demonstrate that the sensitivity of ovarian epithelial tumor cells to CTL-mediated lysis is associated with the level of expression of HER2/neu, suggesting that this oncogene product may serve as a source of tumor-associated Ags or

Gene Symbol: HER2/neu

7/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07716673 93238227 PMID: 8097427

Resistance of HER2/neu-overexpressing tumor targets to lymphokine-activated-killer-cell-mediated lysis: evidence for deficiency of binding and post-binding events.

Fady C; Gardner A; Gera J F; Lichtenstein A

Department of Medicine, VA Wadsworth-UCLA Medical Center 90073.

Cancer immunology, immunotherapy : CII (GERMANY) May 1993, 36

(5) p307-14, ISSN 0340-7004 Journal Code: 8605732

Contract/Grant No.: CA 16042; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

HER2/neu-overexpressing tumor cell lines are relatively resistant to lymphokine-activated killer (LAK) cell cytotoxicity when compared to HER2/neu-nonexpressing lines. HER2/neu + targets were also resistant to binding by LAK large granular lymphocytes (LGL) as shown by visualization at the single-cell level, a target monolayer binding assay and in "cold" target inhibition experiments. HER2/neu + LAK-resistant ovarian cell lines demonstrated an absence of ICAM-1 expression while expression of LFA-3, N-CAM, laminin and beta 1 integrins was comparable to that of HER2/neu- targets. In contrast, the HER2/neu + breast cell line, SKBR-3, which was also resistant to

lysis and binding by LAK LGL, demonstrated normal expression of ICAM-1. Anti-ICAM-1 antibodies blocked binding and lysis of HER2/neu - carcinoma targets by LAK cells, further supporting the notion that lack of ICAM-1 expression on HER2/neu+ cells contributes to their resistance. The modest binding and lysis of HER2/neu+ targets by LAK cells was significantly inhibited by anti-LFA-1 antibodies, suggesting the existence of another counter-receptor for LFA-1 on HER2/neu+ targets. The following also supported deficiencies in post-binding events when HER2/neu + cells resisted the lytic activity of LAK cells: (a) when the relative resistance to effector cell binding was overcome by exogenous lectin. HER2/neu + cell lines were still resistant to LAK cytotoxicity, and (b) HER2/neu + targets were resistant to perforin-containing granule extracts obtained from the CTLL-R8 cytotoxic lymphocyte cell line. These results indicate that deficiency in effector binding as well as post-binding events contributes to the resistance of HER2/neu -overexpressing tumor targets to LAK-cell-mediated lysis.

Resistance of HER2/neu -overexpressing tumor targets to lymphokine-activated-killer-cell-mediated lysis: evidence for deficiency of binding...

May 1993,

HER2/neu-overexpressing tumor cell lines are relatively resistant to lymphokine-activated killer (LAK) cell cytotoxicity when compared to HER2/neu-nonexpressing lines. HER2/neu + targets were also resistant to binding by LAK large granular lymphocytes (LGL) as shown by...

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7/3,K,AB/6 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04022843 Genuine Article#: RA605 Number of References: 31

Title: IDENTIFICATION OF AN IMMUNODOMINANT PEPTIDE OF HER-2/
NEU PROTOONCOGENE RECOGNIZED BY OVARIAN TUMOR-SPECIFIC CYTOTOXIC
T-LYMPHOCYTE LINES (Abstract Available)

Author(s): FISK B; BLEVINS TL; WHARTON JT; IOANNIDES CG

Corporate Source: UNIV TEXAS,MD ANDERSON CANC CTR,DEPT GYNECOL ONCOL,BOX
67,1515 HOLCOMBE BLVD/HOUSTON//TX/77030; UNIV TEXAS,MD ANDERSON CANC
CTR,DEPT GYNECOL ONCOL/HOUSTON//TX/77030; UNIV TEXAS,MD ANDERSON CANC

CTR,DEPT IMMUNOL/HOUSTON//TX/77030

Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1995, V181, N6 (JUN 1), P 2109-2117

ISSN: 0022-1007

Language: ENGLISH Document Type: ARTICLE

Abstract: Synthetic peptide analogues of sequences in the **HER-2** protooncogene (**HER-2**) were selected based on the presence of HLA-A2.1 anchor motifs to identify the epitopes on **HER-2** recognized by ovarian tumor-reactive **CTL**. 19 synthetic peptides were evaluated for recognition by four HLA-A2(+) ovarian-specific cytotoxic T lymphocyte (**CTL**) lines obtained from leukocytes associated with ovarian tumors. The nonapeptide E75 (**HER-2**, 369-377:KIFGSLAFL) was efficient in sensitizing T2 cells for lysis by all four **CTL** lines. This peptide was specifically recognized by cloned CD8(+) **CTL** isolated from one of the ovarian-specific **CTL** lines. E75-pulsed T2 cells inhibited lysis by the same **CTL** clone of both an HLA-A2(+) **HER-2**(high) ovarian tumor and a **HER-2**(high) cloned ovarian tumor line transfected with HLA-A2, suggesting that this or a structurally similar epitope may be specifically recognized by these **CTL** on ovarian tumors. Several other **HER-2** peptides were recognized preferentially by one or two **CTL** lines, suggesting that both common and private **HER-2** epitopes may be immunogenic in patients with ovarian tumors. Since **HER-2** is a self-antigen, these peptides may be useful for understanding mechanisms of tumor recognition by T cells, immunological tolerance to tumor, and structural characterization of tumor antigens.

Title: IDENTIFICATION OF AN IMMUNODOMINANT PEPTIDE OF **HER-2**/
NEU PROTOONCOGENE RECOGNIZED BY OVARIAN TUMOR-SPECIFIC CYTOTOXIC
T-LYMPHOCYTE LINES
, 1995

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...Identifiers--MAJOR HISTOCOMPATIBILITY COMPLEX; **CELL-LINES**;
EXPRESSION; BINDING; PROTEIN; **CANCER**; HLA-A2; MOLECULES;
EPITOPES; RECEPTOR

7/3,K,AB/7 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

02077584 Genuine Article#: JY980 Number of References: 25
Title: ENGINEERING A HUMANIZED BISPECIFIC-F(AB')₂ FRAGMENT FOR IMPROVED

BINDING TO T-CELLS (Abstract Available)

Author(s): RODRIGUES ML; SHALABY MR; WERTHER W; PRESTA L; CARTER P
Corporate Source: GENENTECH INC,DEPT PROT ENGN,460 POIN SAN BRUNOBLVD/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT PROT ENGN,460 POIN SAN BRUNOBLVD/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT MED & ANALYT CHEM/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT IMMUNOL/S SAN FRANCISCO//CA/94080

Journal: INTERNATIONAL JOURNAL OF CANCER, 1992, S7, P45-50

ISSN: 0020-7136

Language: ENGLISH Document Type: ARTICLE

Abstract: We recently constructed a humanized bispecific antibody (BsF(ab')₂v1) by separate E. coli expression of each Fab' arm followed by directed chemical coupling in vitro. BsF(ab')₂ v1 (anti-CD3/anti-p185HER2) was demonstrated to retarget the cytotoxic activity of human CD3+ CTL in vitro against the human breast-tumor cell line, SK-BR-3, which over-expresses the p185HER2 product of the proto-oncogene HER2. Our minimalistic humanization strategy is to install as few murine residues as possible into a human antibody in order to recruit antigen-binding affinity and biological properties comparable to that of the murine parent antibody. This strategy proved very successful for the anti-p185HER2 arm of BsF(ab')₂ v1. In contrast BsF(ab')₂ v1 binds to T cells via its anti-CD3 arm much less efficiently than does the chimeric BsF(ab')₂ which contains the variable domains of the murine parent anti-CD3 antibody. Here we have constructed additional BsF(ab')₂ fragments containing variant anti-CD3 arms with selected amino acid replacements in an attempt to improve antibody binding to T cells. One such variant, BsF(ab')₂ v9, was created by replacing 6 residues in the second hypervariable loop of the anti-CD3 heavy chain variable domain of BsF(ab')₂ v1 with their counterparts from the murine parent anti-CD3 antibody. BsF(ab')₂ v9 binds to T cells (Jurkat) much more efficiently than does BsF(ab')₂ v1 and almost as efficiently as the chimeric BsF(ab')₂. This improvement in the efficiency of T-cell binding of the humanized BsF(ab')₂ is an important step in its development as a potential therapeutic agent for the treatment of p185HER2 over-expressing cancers.

, 1992

...Abstract: v1 (anti-CD3/anti-p185HER2) was demonstrated to retarget the cytotoxic activity of human CD3+ CTL in vitro against the human breast-tumor cell line, SK-BR-3, which over-expresses the p185HER2 product of the proto-oncogene HER2. Our...

...Research Fronts: 1825 002 (C-ERBB-2 ONCOGENE EXPRESSION; EPIDERMAL GROWTH-FACTOR RECEPTORS IN BREAST-CANCER; RAT NEU GENE; HER-2/NEU AMPLIFICATION PREDICTS POOR SURVIVAL)

90-0293 001 (POLYACRYLAMIDE GELS FOR PROTEIN SEQUENCING; POLYVINYLIDENE DIFLUORIDE MEMBRANES...

?